Remarks

Claims 1-8 are pending. Claims 1-8 stand rejected.

Applicants have reviewed the Office Action, including the Examiner's remarks and the references cited therein. Applicants submit that the following remarks are fully responsive to the Office Action, and that all pending claims are patentable over the cited references.

Rejections Under 35 U.S.C. § 103

Claims 1-8 stand rejected under 35 U.S.C. § 103, as allegedly being unpatentable over Ramsby et al. (Electrophoresis, Feb. 1994; 15(2): 265-67, further in view of Robaye et al. (Electrophoresis, 1994; 15:503-510), further in view of Squier et al. (Journal of Cellular Physiology, May 1994; 159(2): 229-237), further in view of Lowe et al. (Nature, 29 April 1993; 362:847-49), further in view of Lane et al. (British Medical Bulletin, 1994; 50(3):582-599). Applicants respectfully disagree.

The claimed method refers to inhibiting p53 degradation. The presence of p53, one of ordinary skill in the art knows, results in or induces apoptosis. Thus, the claimed methods relate, *inter alia*, to fostering apoptotic conditions, such as detecting p53 fragments after administration of peptide or protein inhibitors of calpain protease activity. In contrast, the cited art, as detailed below, refers only to preventing apoptotic conditions.

Although the prior art references need not teach or suggest each and every limitation of a claim for that claim to be obvious, Applicants contend that the differences between the instant claims and the references cited are sufficiently great so as to render the claimed invention non-obvious to one of ordinary skill in the art at the time the invention was made. *See* MPEP § 2141(II) ("[T]he focus when making a determination of obviousness should be on what a person of ordinary skill in the pertinent art would have known at the time of the invention, and on what such a person would have reasonably expected to have been able to do in view of that knowledge"). In particular, as discussed in further detail below, Applicants contend that the cited references fail to teach or suggest at least step 2 of claim 1, *i.e.*, "administering a peptide or protein

inhibitor of calpain protease activity to the cell extract."

Notably, the Examiner has repeatedly relied on the Ramsby reference throughout prosecution. Nevertheless, Ramsby explicitly teaches that EDTA (the alleged calpain inhibitor) is added to digitonin and Triton buffers, and not to a cell extract containing p53 and a protease. Ramsby, p. 268, col. 1, ll. 47-50 ("The addition of EDTA to digitonin and Triton buffers enhances the rate and selectivity of fractionation and prevents undesirable degradation of cellular proteins by calcium-activated proteases"). Significantly, the Examiner explicitly concedes that "Ramsby et al. do not specifically teach administering protein inhibitors of calpain to the cell extract." Office action at p. 7.

None of the remaining references compensate for this deficiency. Squier only mentions calpastatin in the context of explaining potential reasons for changes in the activity of calpain. Of course, this has no connection whatsoever to p53. Squier does not disclose administration of calpastatin or any other inhibitor of calpain protease activity to a cell extract containing p53 as claimed. *See* Squier, p. 235, col. 1, ll. 4-6. Additionally, the Examiner explicitly concedes that "Robaye et al. have not treated the cell extracts with particular proteolysis inhibitors of calpain." Office action at p. 7. Moreover, Lane and Lowe do not even appear to mention calpain or calpastatin. Accordingly, Applicants respectfully request the column/line citation of the reference that the Examiner alleges teaches "administering a peptide or protein inhibitor of calpain protease activity to the cell extract."

Second, both Robaye and Squier teach away from the combination with Ramsby, Lowe, and Lane asserted here. The Federal Circuit has explicitly stressed that "[i]t is improper to combine references where the references teach away from their combination." *In re Grasselli*, 713 F.2d 731, 743 (Fed. Cir. 1983). Specifically, Squier discloses that "[p]reincubation with calpain inhibitors *prevented apoptosis* in thymocytes whether induced by dexamethasone or by low-level irradiation," and that "calpain is necessary for triggering apoptosis." Squier, col. 2, ll. 25-26 (emphasis added). One of skill in the art would understand that the claimed methods inhibit p53 degradation, which would result in the opposite effect – p53-induced apoptosis.

Similarly, Robaye teaches that "a role for proteolysis in apoptosis is supported by evidence of increased protease activity during apoptopic regression and by the ability of protease inhibitors to block apoptosis in some cases." Robaye, p. 503, col. 2, lines 6-10 (emphasis added). These disclosures are completely at odds with the purposes of Applicants' invention. Indeed, one of the objects of Applicants' invention is to *trigger apoptosis* in tumor cells by using calpain inhibitors to prevent calpain degradation of wild-type p53. *See* paragraphs [0007], [0011]. There is no explanation for the contradictory statements from Robaye or Squier.

Thus, in view of the references cited by the Examiner, the skilled artisan would have absolutely no reason to combine p53 (mentioned briefly in Ramsby, Lowe, and Lane) with calpain and calpastatin (discussed in Robaye and Squier) if the artisan's goal was to trigger apoptosis in tumor cells. One of skill in the art understands the presence of p53 in cells triggers apoptosis. So, the steps of the claimed method are the opposite of what Robaye and Squier teach and suggest one to do.

Indeed, the Examiner concedes that "none of the above references specifically indicate that p53 is a substrate of calpain." Office action at p. 8 (emphasis added). If there is some other logical reason for combining these alleged teachings, it has not been expressed on the record. Instead, based on the teachings of Robaye and Squier, the skilled artisan would be led in an opposite direction. Thus, because the Robaye and Squier references teach away from a combination with the Ramsby, Lowe, and Lane references, Applicants submit that any alleged obviousness has been rebutted.

Third, Lane expressly teaches away from the claimed invention. Notably, the Federal Circuit has emphasized that references that teach away from the claimed invention cannot serve to create a *prima facie* case of obviousness. *McGinley v. Franklin Sports, Inc.*, 262 F.3d 1339, 1354 (Fed. Cir. 2001) (citing *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994)) (noting that "as a 'useful general rule,' [ ] references that teach away cannot serve to create a *prima facie* case of obviousness"); *see also* MPEP § 2141.02 ("A prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention"). "A 'reference will teach away if it suggests that the line of development flowing from the reference's

disclosure is unlikely to be productive of the result sought by the applicant.'" *Winner Int'l Royalty Corp. v. Wang*, 202 F.3d 1340, 1350 (Fed. Cir. 2000) (citing *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994)).

In particular, Lane teaches that "the HPV E6 protein also acts to promote the rapid breakdown of p53 by specifically targeting its destruction through the ubiquitin pathway." Lane, p. 592, ll. 18-21. The ubiquitin pathway involves tagging substrates with ubiquitin and destruction of the tagged proteins by the 26S proteasome—an entirely different pathway than the calpain degradation pathway described in our application. Thus, a person of skill in the art would have not looked to Lane to arrive at the claimed invention.

Fourth, the Examiner disregards the basic precept that obviousness is to be determined by looking at the claimed invention and the prior art references as a whole, and not by looking at the individual differences themselves. "In determining the differences between the prior art and the claims, the question under 35 U.S.C. § 103 is not whether the differences themselves would have been obvious, but whether the claimed invention as a whole would have been obvious." MPEP § 2141.02 (citing *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530 (Fed. Cir. 1983)). Moreover, the MPEP provides that "[a]scertaining the differences between the prior art and the claims at issue requires interpreting the claim language, and considering both the invention and the prior art references as a whole." MPEP § 2141.02.

The Ramsby reference, when viewed as a whole, demonstrates the nonobviousness of the present invention. Specifically, Ramsby discusses a method for "differential detergent fractionation (DDF) which reproducibly partitions hepatocytic proteins into four distinct fractions and appears to preserve cytoskeletal interactions." Ramsby, page 266, column 1, lines 48-52. The Examiner has provided no explanation as to why the skilled artisan would even consult this reference, or consider its teachings remotely relevant to detecting an inhibitor of p53 protein degradation. Rather, the Examiner merely highlights the presence of terms common to the reference and to the claims at issue, without providing a detailed rationale as to why the reference as a whole should even enter the equation. Applicants respectfully request that the

Examiner explain why a person having ordinary skill in the art in the field would consult a source discussing differential detergent fractionation of hepatocytes.

For at least these reasons, Applicants respectfully submit that a *prima facie* case of obviousness has not been established. Having addressed each outstanding rejection and objection, Applicants request allowance of the application.

CONCLUSION

Applicants respectfully request entry of the amendments and timely notification of allowability. If there are any additional fees due with the filing of this document, or any attached document, including fees for the net addition of claims, applicants respectfully request that any and all fees be charged to Deposit Account No. 50-1129. If any extension of time request or any petition is required for the entry of this paper or any of the accompanying papers, applicants hereby petition or request the extension necessary. The undersigned authorizes any fee payment from Deposit Account No. 50-1129. Furthermore, if additional extensions of time are required to enter this amendment beyond any provided for, applicants respectfully request an extension and the undersigned hereby authorizes that any fees be taken from Deposit Account No. 50-1129, referencing Attorney Docket No. 80375.0033.

Respectfully submitted,

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Date: October 21, 2009

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